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ORIGINAL ARTICLE

Trans-vaginal sono-elastography in the differentiation of endometrial hyperplasia and endometrial carcinoma

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KEYWORDS

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Abstract *Aim:* To evaluate efficiency of sono-elastography in differentiation of endometrial hyperplasia and endometrial carcinoma.
Patients and methods: Between January 2014 and January 2015, 45 perimenopausal female patients with endometrial thickness more than 6 mm were examined by TV sono-elastography procedure. Results of ultrasound and elastography were compared with pathological data (reference standard). Strain ratios were compared between typical, atypical endometrial hyperplasia and endometrial carcinoma. Accuracies of SR in differentiating hyperplasia and endometrial cancer were assessed with the Student *t* test, and cutoff values were determined with receiver operating curve analysis.
Results: There was statistically significant difference between mean SR ratio of endometrial carcinoma (11.4) and endometrial hyperplasia (2.7) ($P < 0.001$). Mean SR of atypical endometrial hyperplasia (5.6) was significantly higher than that of typical endometrial hyperplasia (1.9) ($P < 0.001$). SR of 7.2 as a cutoff value resulted in 92.3% sensitivity, 100% specificity and 97.8% accuracy for differentiation between endometrial carcinoma and endometrial hyperplasia and SR of $\leqslant 4$ as a cutoff value resulted in 100% sensitivity, 85.7% specificity and 96.9% accuracy in differentiation between typical and atypical endometrial hyperplasia.
Conclusion: TV sono-elastography can aid in differentiation of typical, atypical endometrial hyperplasia and endometrial cancer.

1. Introduction

Endometrial hyperplasia is characterized by a proliferation of endometrial glands resulting in a greater gland-to-stroma ratio than observed in normal endometrium. Several different terms were utilized to signify abnormal proliferation of the endometrium. These terms included the following: ‘‘adenomatous

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Table 1 Endometrial thickness and SR in cases of endometrial carcinoma and endometrial hyperplasia.

Pathology	Age	Endometrial thickness	SR	*N*
Hyperplasia				
Minimum–maximum	48.00–72.00	8.00–22.00	0.90–7.20	32
Mean ± standard deviation	59.34 ± 6.89	14.87 ± 4.09	2.75 ± 1.81	
Carcinoma				
Minimum–maximum	50.00–68.00	14.00–34.00	6.00–16.00	13
Mean ± standard deviation	59.46 ± 5.82	21.92 ± 5.88	11.40 ± 3.05	
Total				
Minimum–maximum	48.00–72.00	8.00–34.00	0.90–16.00	45
Mean ± standard deviation	59.37 ± 6.53	16.91 ± 5.62	5.25 ± 4.53	
P value	0.96	< 0.001	< 0.001	

Table 2 Endometrial thickness and SR in cases of typical and atypical endometrial hyperplasia.

Pathology	Age	Endometrial thickness	SR	*N*
Typical hyperplasia				
Minimum–maximum	48.00–72.00	8.00–22.00	0.90–4.00	25
Mean ± standard deviation	59.04 ± 6.82	14.44 ± 4.14	1.96 ± 0.82	
Atypical hyperplasia				
Minimum–maximum	49.00–70.00	10.00–21.00	2.90–7.20	7
Mean ± standard deviation	60.42 ± 7.59	16.42 ± 3.77	5.60 ± 1.49	
Total				
Minimum–maximum	48.00–72.00	8.00–22.00	0.90–7.20	32
Mean ± standard deviation	59.34 ± 6.89	14.87 ± 4.09	2.75 ± 1.81	
P value	0.65	0.26	< 0.001	

hyperplasia", "atypical hyperplasia", and "carcinoma in situ." Because the criteria for many of the terms were never clearly standardized, the relationship between proliferative endometrial lesions and carcinoma was not always apparent (1).

Carcinoma of the endometrium is among the most common female pelvic malignancies and may develop in normal, atrophic, or hyperplastic endometrium (2,3). The most common histologic type, endometrioid adenocarcinoma (ECa), accounts for 75–80% of diagnoses and commonly is associated with long-term, unopposed estrogenic stimulation (4).

Majority of endometrioid neoplastic lesions of the endometrium follow a continuum of histologically distinguishable hyperplastic lesions that cover a spectrum ranging from endometrial hyperplasia without atypia (EH), to endometrial hyperplasia with atypia (AEH), to well differentiated ECa (5). However, this continuum of endometrial hyperplasia has not undergone the same degree of rigorous, prospective, multicenter evaluation as other classification systems for preinvasive neoplastic lesions, such as cervical neoplasia (4).

The prognosis for women with endometrial cancer is generally good. However, the prognosis is worse for women with high-risk endometrial cancer (6).

Elastography is an ultrasound technique that measures stiffness of tissue. It is based on differences in the elasticity of various tissues, in both physiological and pathological conditions. To obtain an elastography image it is necessary to have a source of stress that provides deformation of the tissue (7).

Elastograms are images of tissue stiffness and may be in color, grayscale, or a combination of the two. Recent advances in elastography include quantification using strain ratios, acoustic radiation force impulse imaging, and shear wave velocity estimation (8).

Promising results regarding the use of elastography have been described in the assessment of tumors of the breast, prostate and liver (9–13). However, publications on the use of elastography in the field of gynecology are scarce (7).

2. Aim of the work

The aim of the work was to evaluate the role of TV sonoelastography in prediction of endometrial carcinoma and its differentiation from endometrial hyperplesia.

3. Patients and methods

3.1. Patients

Between the periods of January 2014 and January 2015, this prospective study was conducted on 45 perimenopausal female patients, with age ranging from 48 to 72 years and mean age of 59.3 years. Inclusion criterion was endometrial thickness of more than 6 mm. Patients with myometrial invasion, history of previous surgery, radiotherapy or dilatation and curettage (D & C) were excluded to ensure accurate results. Informed

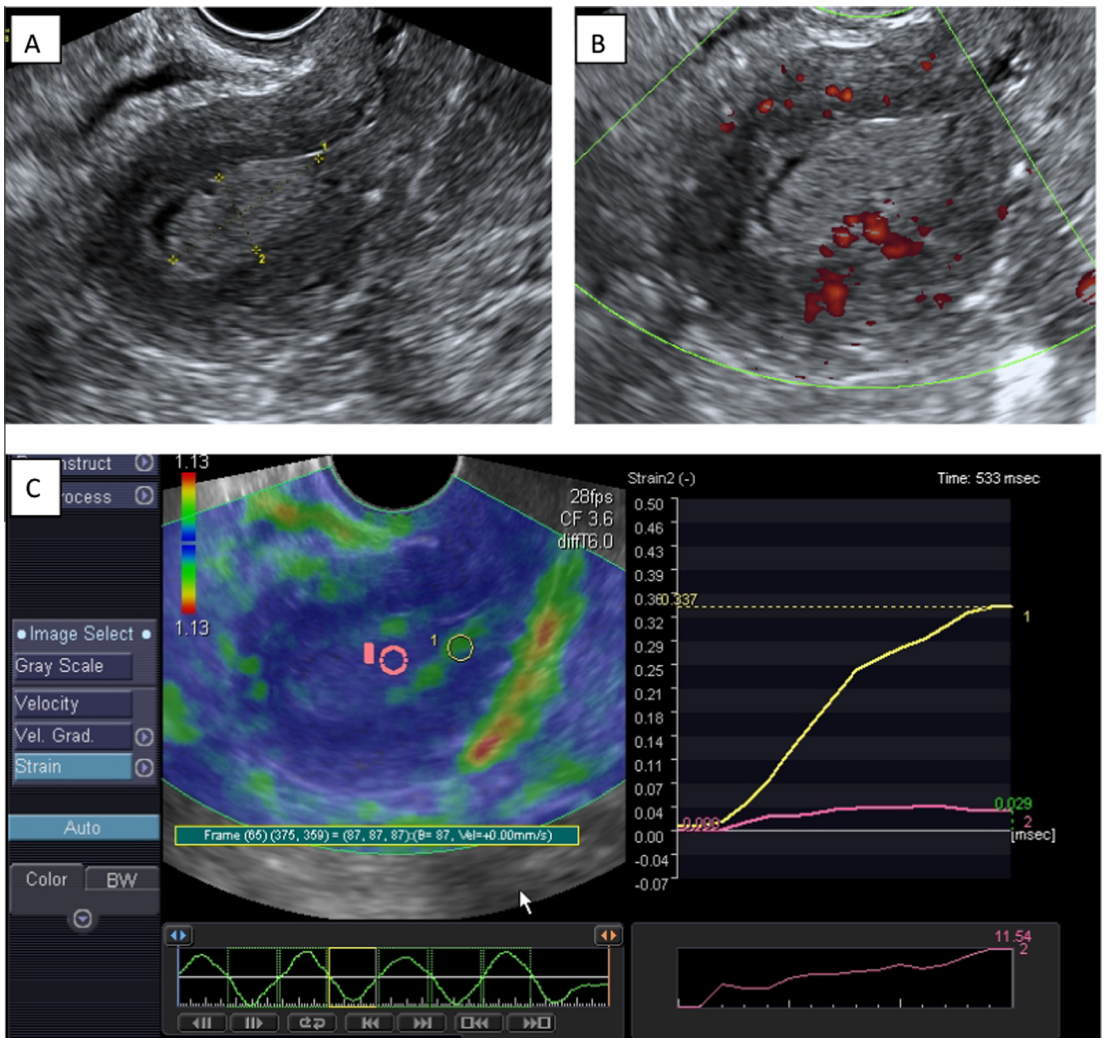


Fig. 1 Ultrasound images of a female patient, aged 55 years with malignant thickened endometrium (confirmed to be endometrial adenocarcinoma by pathological examination). B-mode ultrasound image (A), Power Doppler image (B) and TV elastogram (C) show endometrial thickness = 18 mm with increase vascularity, dark blue color and SR = 11.54.

consents required by the human study committee were taken from all enrolled patients.

3.2. Methods

TV sonoelastography was done for all patients, and then biopsy or surgery was done according to the case.

3.2.1. Acquisition of the elastograms

Transvaginal US scanning including sonoelastography and 3D/4D technology was performed by using aplio XG system (Toshiba Medical System, Tokyo, Japan) with a frequency of 5–8 MHz endo-vaginal probe. All the examinations were performed by 2 independent radiologists (M. A and M. S). The first radiologist had more than 19 years and the second had about 25 years' experiences in ultrasonic scanning. To avoid the interobserver variability, the examination was done by one of the 2 observers in attendance of the other, and the results were recorded by consensus. They were blinded to the physical examination, and other investigation was done for the patients.

Patients were asked to empty bladder and lie in lithotomy position. A disposable condom was used to prevent cross infection. The TV ultrasound probe was put into the vagina about 1 cm away from the cervix. The uterus was scanned in the coronal and longitudinal projections. The thickest anteroposterior diameter of the endometrial stripe was measured in the sagittal plane. Color Doppler was used to assess the blood supply of the lesions. The highest sensitivity for detection of color Doppler signals was used, allowing detection of blood flow velocities $\geqslant 2$ cm/s. Then, elastography mode was chosen to evaluate the stiffness of the endometrial stripe. Support of the anterior pelvic wall was done by the operator's left hand and manual compression on the endometrium by his right hand. Manual compression was standardized as the most uniform waveform was obtained and the most symmetrical waveforms were selected.

The parameters were set as follows: density 2; frame rate M; dynamic range 6; Persistence 5; smoothing 2; noise rejection 2; frame rejection 3. To define the sonoelastography patterns and the comparative analysis, we used the visual grading system proposed by Thomas et al. (14), as the elastography images were analyzed by means of a software tool to identify thresh-

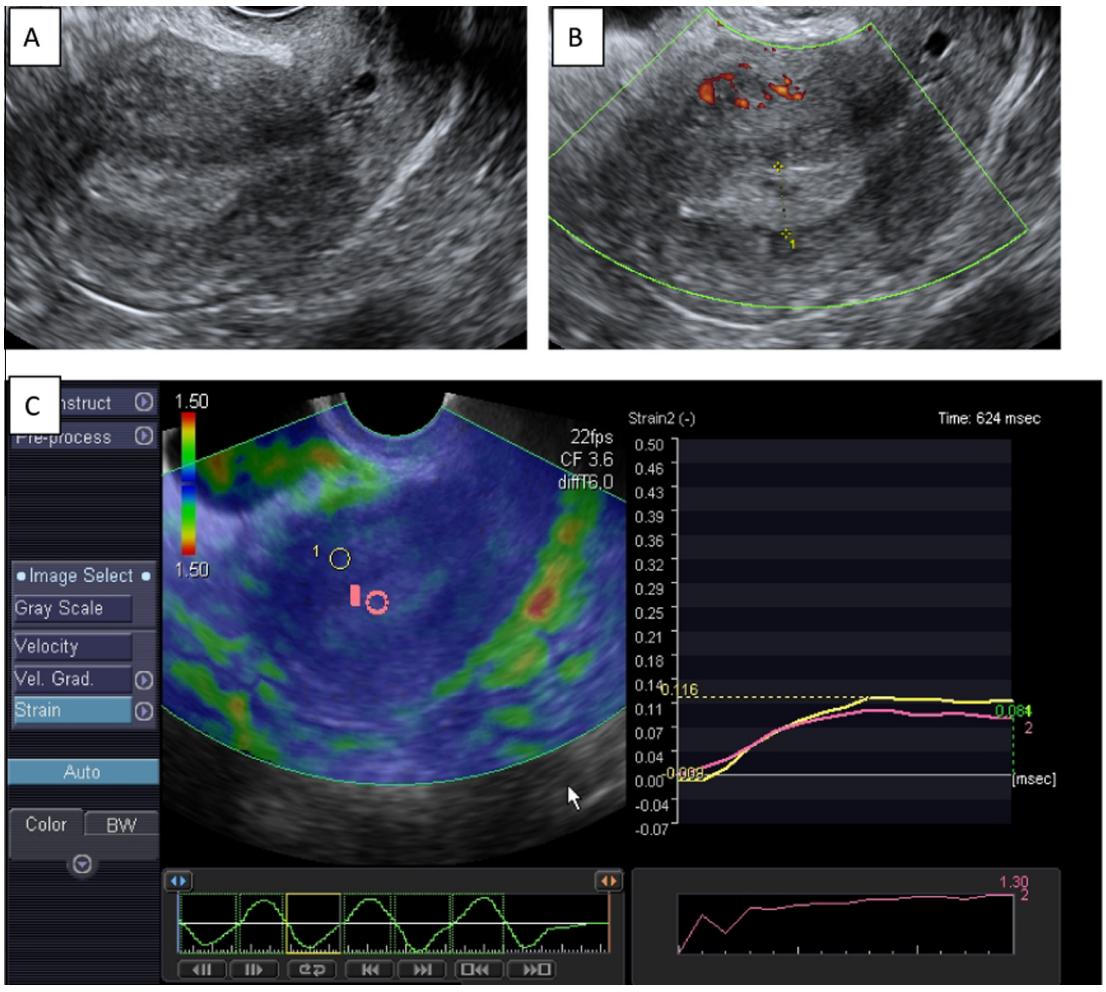


Fig. 2 Ultrasound images of a female patient, aged 60 years with thickened endometrium (confirmed to be typical endometrial hyperplasia by pathological examination). B-mode ultrasound image (A), Power Doppler image (B) and TV elastogram (C) show endometrial thickness = 12 mm with no significant increase vascularity, green to light blue color and SR = 1.3.

olds for the colors red (soft), blue (hard), and green (medium hard), and the percentages of the three colors of the total area were determined. On average, 3 (range 2–5) clips and 4 (range 3–6) static images were obtained for each patient. The standard reference ROI was the myometrium.

3.2.2. Evaluation of the elastograms

Strain ratio was carried out to evaluate the hardness of the endometrium half-quantitatively. All patients were assessed at least 3 times by 2 of the independent observers (M. A and M. S), based on different static images and the average strain ratios were recorded as their final results. Both of the observers were blind to the physical and pathological results.

The results of ultrasound study and elastography were compared with pathological data.

3.2.3. Statistical analysis

Statistical analysis was carried out via Statistical package for social Science (SPSS) version 17 program on windows XP. Qualitative data were represented in the form of number and frequency, while quantitative data were represented in the form of mean ± standard deviation (mean ± SD). Kolmogorov–Smirnov test was used to test normality of quantitative data. Student's t test, Mann–Whitney U and Kruskal–Wallis Test were used to compare groups. Receiver operating characteristic (ROC) curve was computed to determine the cutoff value for the malignancy. All tests were considered significant if P value equals or less than 0.05.

4. Results

This study included 45 patients: thirty-two patients had endometrial hyperplasia (25 patients with typical and 7 patients with atypical endometrial hyperplasia), and their ages ranged from 48 to 72 years with mean age of 59.4 years. Thirteen patients had endometrial carcinoma with their ages ranging from 50 to 68 years and mean age of 59.5 years (Table 1).

The mean endometril thickness of patients with endometrial carcinoma was 21.9 mm and mean endometrial thickness of patients with endometrial hyperplasia was 14.8 mm. There was no statistically significant difference in endometrial thickness between patients with typical and atypical endometrial hyperplasia (Table 2).

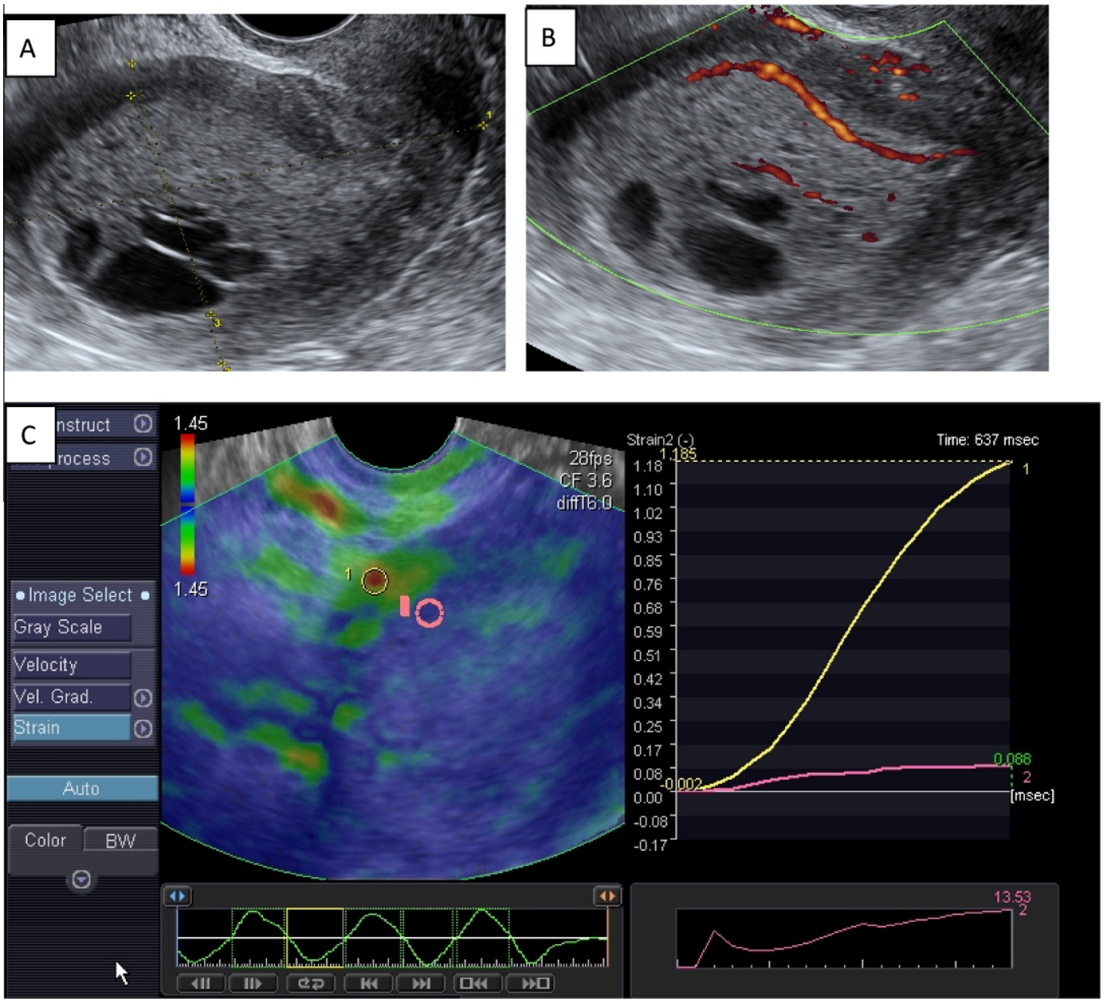


Fig. 3 Ultrasound images of a female patient, aged 62 years with malignant thickened endometrium (confirmed to be endometrial adenocarcinoma by pathological examination). B-mode ultrasound image (A), Power Doppler image (B) and TV elastogram (C) show endometrial thickness = 34 mm with increase vascularity, dark blue color and SR = 13.53.

The mean SR of endometrial carcinoma (Fig. 3) =11.4 was significantly higher than endometrial hyperplasia (Fig. 5) =2.7, with $P < 0.001$ (Table 1).

Mean SR ratio of typical endometrial hyperplasia (Fig. 2) was 1.9, while mean SR of atypical endometrial hyperplasia (Fig. 4) was 5.6 with significant statistical difference ($P < 0.001$) (Table 2).

Nine of the 13 endometrial carcinomas had high vascularity, while 18 of the 32endometrial hyperplasia patients showed no significant vascularity at power Doppler imaging.

On color scale, there was significant difference between patients with endometrial carcinoma and patients with endometrial hyperplasia ($P < 0.001$) as 11 of the 13 endometrial carcinomas showed dark blue color (Fig. 1) with 2 showing light blue with no green or yellow color, while out of the 32 endometrial hyperplasia patients, 2 had dark blue, 20 had light blue (Figs. 4 and 5), 8 had green to light blue (Fig. 2) and 2 had green color (Table 3).

There was no statistical difference in color scale between typical and atypical endometrial hyperplasia.

Using the SR of 7.2 as a cutoff value resulted in 92.3% sensitivity, 100% specificity and 97.8% accuracy for differentiation between endometrial carcinoma and endometrial hyperplasia (Table 4).

Using the SR of $\leqslant$4 as a cutoff value resulted in 100% sensitivity, 85.7% specificity and 96.9% accuracy in differentiation between typical and atypical endometrial hyperplasia (Table 5).

5. Discussion

There are only a few reports in the literature on the in vivo use of real-time transvaginal elastosonography in the field of gynecology. The usefulness of this technique has been documented for breast cancer and liver fibrosis, and has been of interest in the exploration of malignant tumors in the cervix, prostate and thyroid (14–19).

Endovaginal ultrasonography is safe, accessible and inexpensive, and remains the primary imaging method for gynecological evaluation. Real-time elastosonography offers complementary diagnostic and mapping information. It is easy to perform, and the procedure requires only a few seconds of manipulation (20).

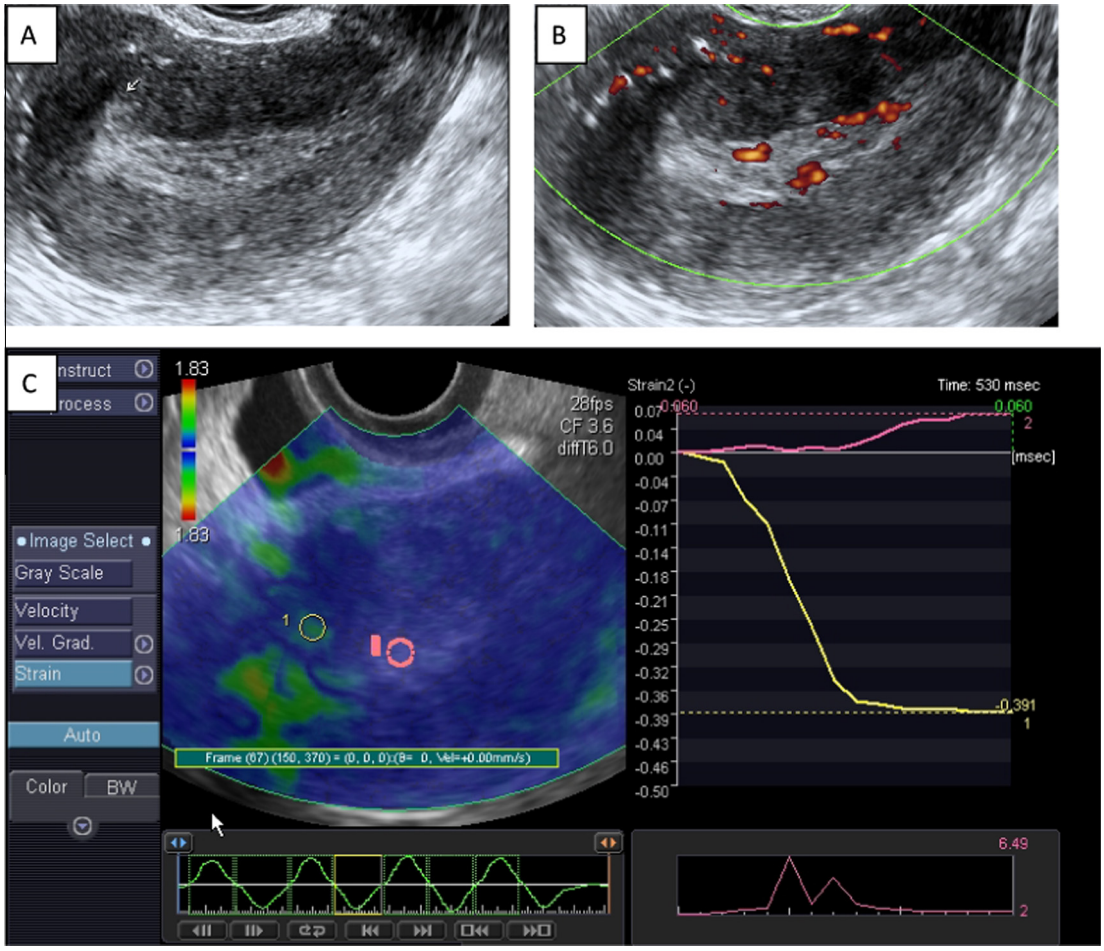


Fig. 4 Ultrasound images of a female patient, aged 63 years with thickened endometrium (confirmed to be atypical endometrial hyperplasia by pathological examination). B-mode ultrasound image (A), Power Doppler image (B) and TV elastogram (C) show endometrial thickness = 17 mm with mild increase vascularity, light blue color and SR = 6.49.

Many researches were done to differentiate normal or atrophic endometrium from pathological endometrium (hypertrophy, polyp, fibroid or cancer). However, to the best of our knowledge, there are only few studies dealing with the topic of differentiation of endometrial hyperplasia and endometrial carcinoma.

Preis et al. (21) concluded that elastography as a new diagnostic technique in gynecology seems to be a valuable tool differentiating endometrial pathologies from normal or atrophic endometrium in perimenopausal women with endometrium thickness above 5 mm in transvaginal ultrasound examination. They found that statistical analysis revealed significant difference of elastography image between patients with normal or atrophic endometrium confirmed by pathological examination and women with abnormal findings – endometrial cancer, hypertrophy or polyp ($P = 0.00005$). Elastography index in the group with normal endometrium was 0 or 1 point and in the group with endometrial pathology was from 2 to 4 points. No patient with elastography index for endometrium above 1 point had normal or atrophic endometrium and no woman with index 0 or 1 had any pathological finding. Another study by Preis et al. (22) found that the difference was significant between normal and pathological endometrium ($P < 0.0001$). The sensitivity of the Elastography Index of endometrium was 100%. So, in patients with endometrium thickness of more than 5 mm but with elastography index below 2 points, unnecessary endometrial biopsy could be avoided in these women.

Ami et al. (23) confirmed that real-time elastosonography is a promising tool that can provide detailed mapping and characterization of uterine fibroids. This could improve the gynecological ultrasound evaluation of size, volume and delineation of uterine fibroids before surgery or embolization. Future studies should aim to investigate strain contrast differences between fibroids and adenomyomas, and the characterization of uterine or adnexal pathologies. They found that the mean strain value was 0.08% for uterine fibroids and 0.77% for the normal surrounding myometrium, giving a myometrium-to-fibroid strain ratio of 11 ($P = 0.017$). All fibroids were seen easily on the color display in elastography mode, and their extent was easier to define than it was in conventional B-mode. The distance between the fibroid and the endometrial cavity or uterine serosa could also be measured easily in each case.

Goncharenko et al. (24) stated that trans-vaginal sonography in complex application with sono-elastography is a highly diagnostic screening test for endometrial pathology. They found that hypoechoic areas, hypervascularity on Doppler

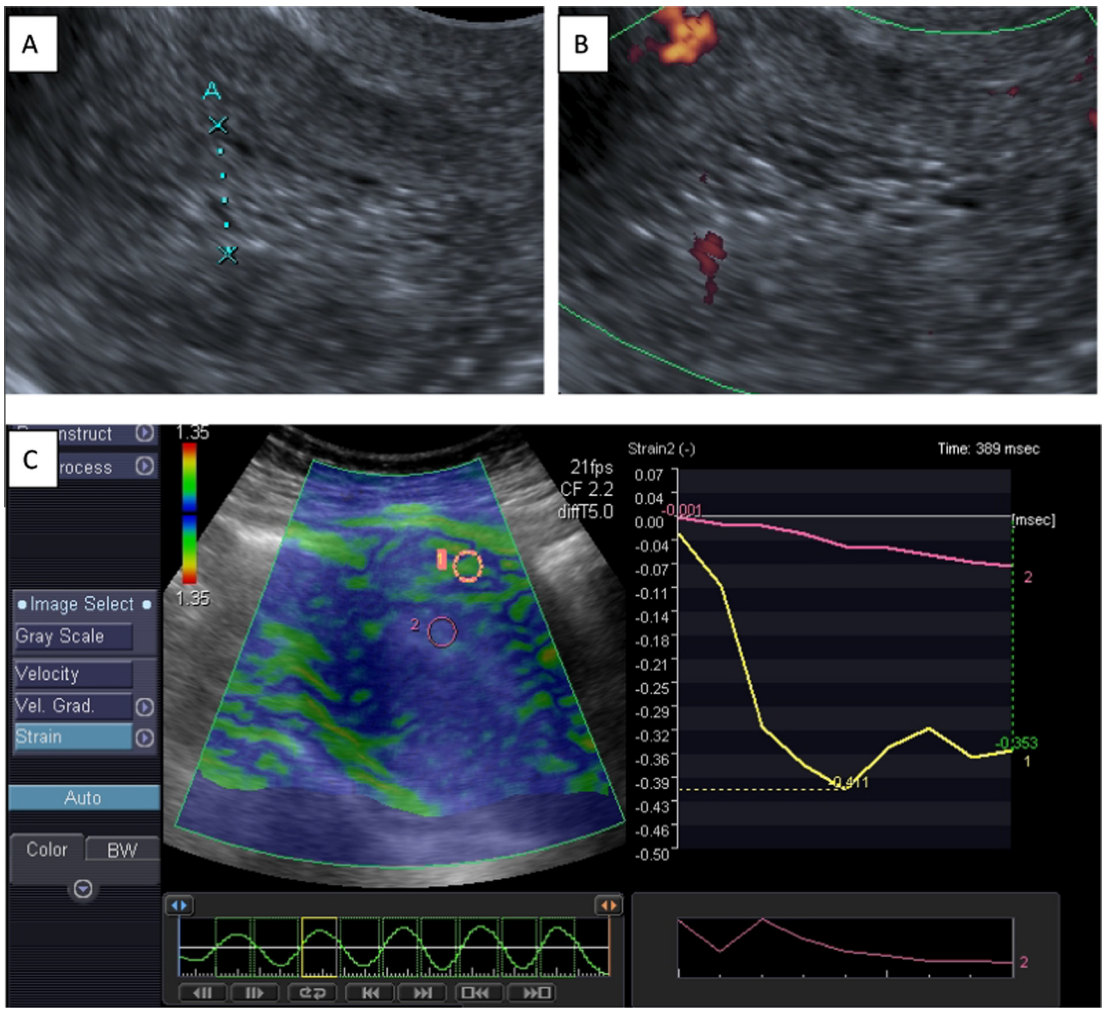


Fig. 5 Ultrasound images of a female patient, aged 55 years with thickened endometrium (confirmed to be typical endometrial hyperplasia by pathological examination). B-mode ultrasound image (A), Power Doppler image (B) and TV elastogram (C) show endometrial thickness = 15 mm with no significant increase vascularity, light blue color and SR = 2.

Table 3 Different color scale in cases of endometrial hyperplasia and endometrial carcinoma.

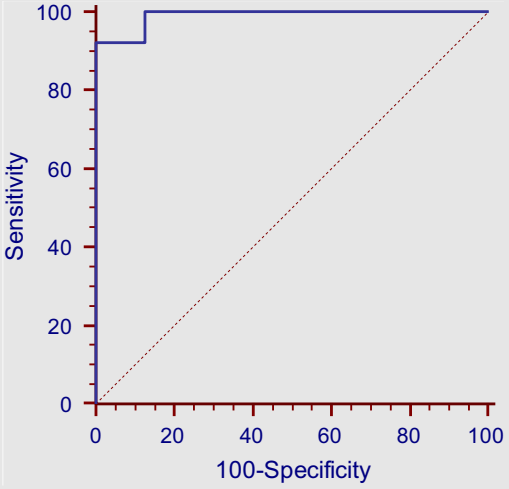
Pathology		Color				Total
		Dark blue	Light blue	Green to light blue	Green	
Hyperplasia	Count	2	20	8	2	32
	%	6.2	62.5	25.0	6.2	100.0
Carcinoma	Count	11	2	0	0	13
	%	84.6	15.4	.0	.0	100.0
Total	Count	13	22	8	2	45
	%	28.9	48.9	17.8	4.4	100.0
P value		< 0.001				

imaging, and stiffness were more specific for AEH than those for glandular cystic hyperplasia ($P < 0.01$, $P < 0.01$, $P < 0.01$, respectively).

In the current study, on color scale: despite there was no significant statistical difference between typical and atypical endometrial hyperplasia. However, there was significant difference between patients with endometrial carcinoma and patients with endometrial hyperplasia ($P < 0.001$).

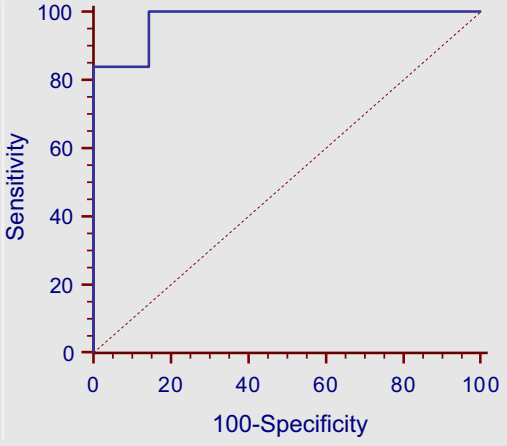
In the present study, when the SR of 7.2 used as a cutoff value resulted in 92.3% sensitivity, 100% specificity and 97.8% accuracy for differentiation between endometrial carcinoma and endometrial hyperplasia, while in the study by Gazhonova et al. (25) the sensitivity and specificity of sonoelastography in the diagnosis of endometrial cancer were 87.8% and 86.9%, respectively. More recently Metin et al. (26) found that TV sonoelastography had a sensitivity of

Table 4 Best SR cutoff value for differentiation of endometrial hyperplasia and endometrial carcinoma (carcinoma vs. hyperplasia).



Cut off	AUC ± SE	95%CI	Sensitivity	Specificity	Accuracy	PPV	NPV
> 7.2	0.99 ± 0.01	0.903–1.000	92.3 (64.0–99.8)	100 (64.0–99.8)	97.8 (85.7–97.8)	100 (77.3–100)	97.0 (88.7–97.0)

Table 5 Best SR cutoff value for differentiation of typical and atypical endometrial hyperplasia (typical vs atypical endometrial hyperplasia).



Cut off	AUC ± SE	95%CI	Sensitivity	Specificity	Accuracy	PPV	NPV
⩽4	0.98 ± 0.03	0.851–1.000	100 (86.3.0–100)	85.7 (64.0–99.8)	96.9 (81.7–96.9)	96.2 (86.6–96.2)	100 (59.4–100)

81.3%, a specificity of 100%, a positive predictive value of 100% and a negative predictive value of 70% in differentiating endometrial carcinoma from endometrial hyperplasia

In our study, using the SR of ⩽4 as a cutoff value resulted in 100% sensitivity, 85.7% specificity and 96.9% accuracy in differentiation between typical and atypical endometrial hyperplasia. So, in patients with thickened endometrium more than 6 mm, but SR ⩽ 4, unnecessary biopsy could be avoided.

5.1. Limitations

This study included small number of patients, so we hope that it is considered as a promising preliminary study to aid in this issue of contra verse which is differentiation of endometrial carcinoma and endometrial hyperplasia. It needs further investigation on large scale of patients.

6. Conclusion

Adding elastography to the TV-sonography is a valuable tool in the diagnosis endometrial pathology and can aid in the differentiation of typical, atypical endometrial hyperplasia and endometrial cancer.

TV sono-elastography can be used as an additional tool to other used screening modalities. Large scale research is needed to assess its use to limit biopsy only if endometrial SR > 4.

Conflict of interest

The authors declare that there are no conflict of interests.

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